

Figure 1



09858289 . 032003

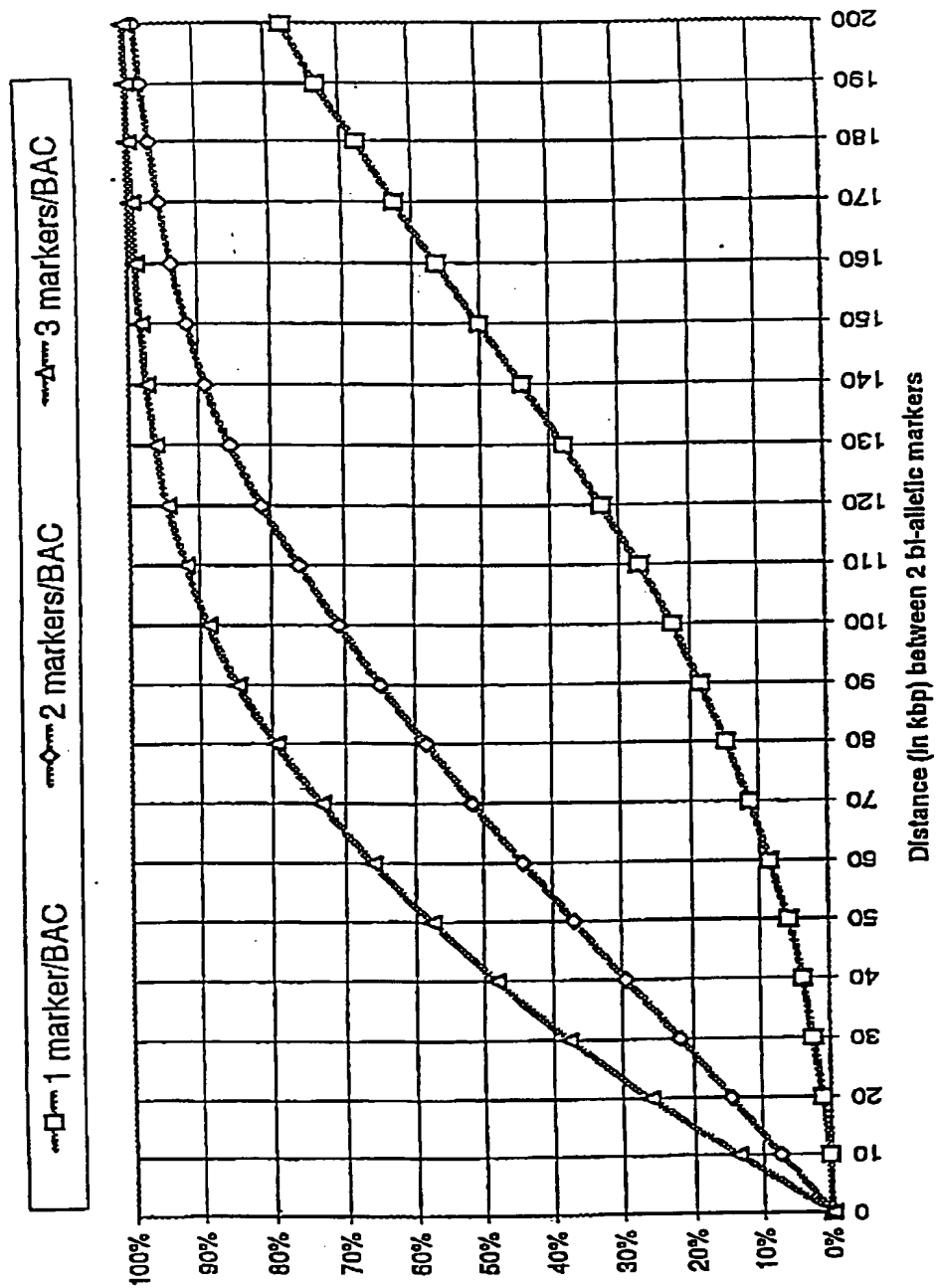


Figure 2A



09858289.032003

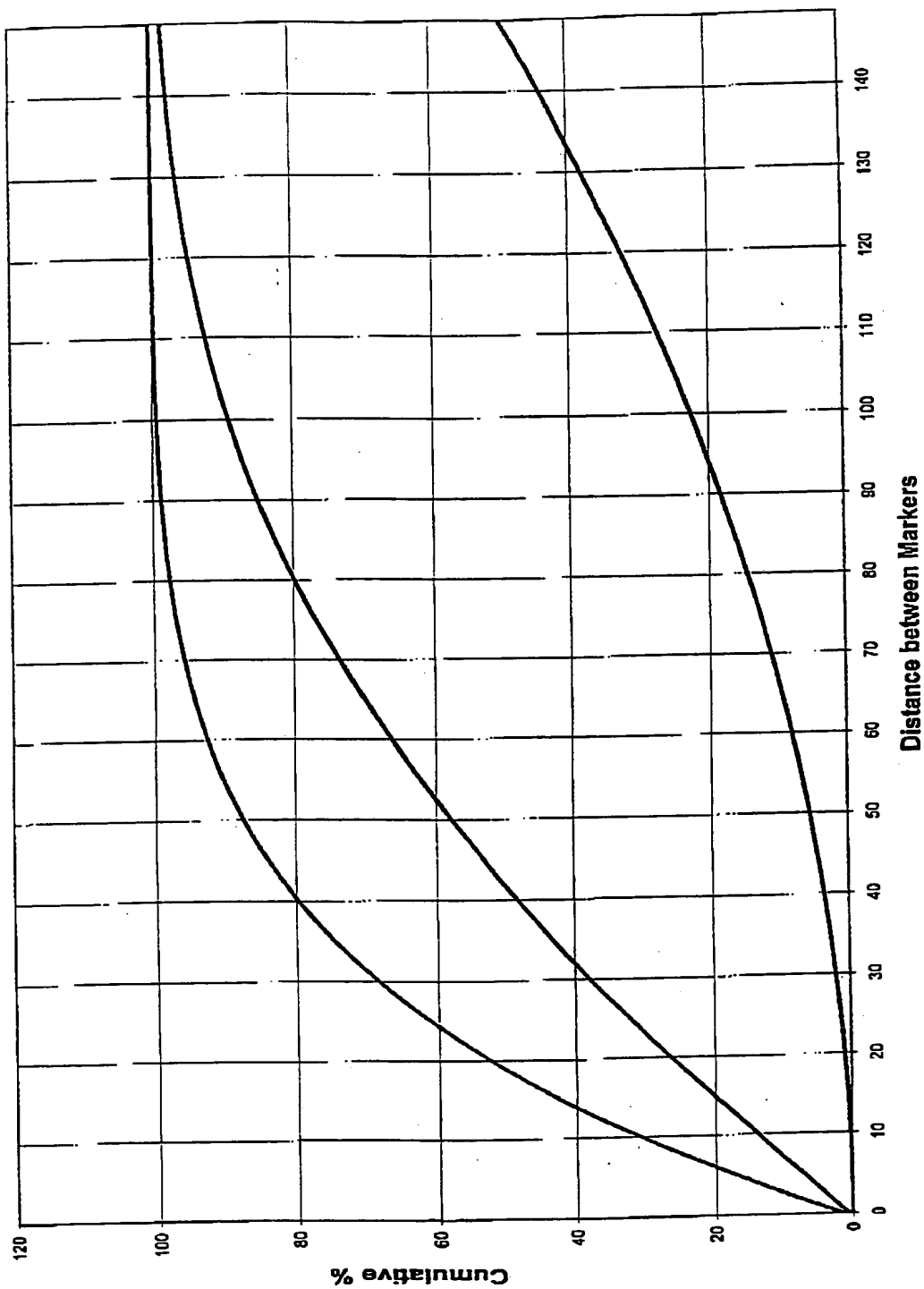


Figure 2B

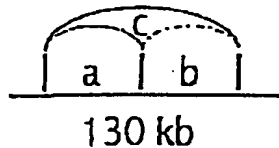
— 1 marker/BAC
— 3 markers/BAC
— 6 markers/BAC



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LD in a random French caucasian population

- 54 sized « random » BACs covering 8100 kb
- 213 SNP ; 2 to 6 / BAC, mean allele frequency = 0.3
- Order and distance unknown
- For 1 BAC :



* \overline{m} intermarker distance : $130/3 = 43$ kb

* \overline{m} LD strength estimate : $m(a,b,c) = 0.51$

- For 54 BACs :

* \overline{m} intermarker distance = 38 kb

* \overline{m} LD strength estimate = 0.63 ± 0.05
(324 pairs)

- For 19 unlinked SNPs : m LD strength estimate = 0.12 ± 0.007
(171 pairs)

Figure 2c



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p-VALUE DISTRIBUTION

| # aff | 150 | | | | | | | | | | |
|-----------|-----|---------|----------|------------|------------|------------|------------|------------|--|--|--|
| # non aff | 150 | | | | | | | | | | |
| | pAi | non aff | 0 | 0,1 | 0,2 | 0,3 | 0,4 | 0,5 | | | |
| Δ pAi | | 0,05 | 8,77E-05 | 0,06407752 | 0,14252002 | 0,19106311 | 0,21543442 | 0,22009395 | | | |
| Δ pAi | | 0,1 | 1,91E-08 | 0,00080384 | 0,00467774 | 0,01023571 | 0,01382303 | 0,01382303 | | | |
| Δ pAi | | 0,15 | 3,06E-12 | 1,3319E-06 | 3,8827E-05 | 0,0001478 | 0,0002343 | 0,00020218 | | | |
| Δ pAi | | 0,2 | 3,22E-16 | 9,1413E-10 | 9,0305E-08 | 5,733E-07 | 9,6338E-07 | 5,733E-07 | | | |
| Δ pAi | | 0,25 | 2,08E-20 | 2,2614E-13 | 6,2679E-11 | 5,873E-10 | 8,7113E-10 | 2,5396E-10 | | | |
| Δ pAi | | 0,3 | 7,82E-25 | 2,152E-17 | 1,3261E-14 | 1,5189E-13 | 1,5189E-13 | 1,3261E-14 | | | |
| Δ pAi | | 0,35 | 1,62E-29 | 7,9823E-22 | 8,4152E-19 | 9,1669E-18 | 4,2713E-18 | 5,5844E-20 | | | |
| Δ pAi | | 0,4 | 1,73E-34 | 1,1282E-26 | 1,524E-23 | 1,1488E-22 | 1,524E-23 | 1,1282E-26 | | | |

| # aff | 200 | | | | | | | | | | |
|-----------|-----|---------|----------|------------|------------|------------|------------|------------|--|--|--|
| # non aff | 200 | | | | | | | | | | |
| | pAi | non aff | 0 | 0,1 | 0,2 | 0,3 | 0,4 | 0,5 | | | |
| Δ pAi | | 0,05 | 5,92E-06 | 0,03250945 | 0,09039173 | 0,13111935 | 0,15260313 | 0,15678006 | | | |
| Δ pAi | | 0,1 | 8,65E-11 | 7,4765E-05 | 0,00109084 | 0,00302886 | 0,00447365 | 0,00447365 | | | |
| Δ pAi | | 0,15 | 8,02E-16 | 2,3653E-08 | 2,0257E-06 | 1,1771E-05 | 2,1573E-05 | 1,7772E-05 | | | |
| Δ pAi | | 0,2 | 4,18E-21 | 1,5375E-12 | 6,7374E-10 | 7,764E-09 | 1,5417E-08 | 7,764E-09 | | | |
| Δ pAi | | 0,25 | 1,13E-26 | 2,525E-17 | 4,4025E-14 | 8,5532E-13 | 1,4423E-12 | 2,8148E-13 | | | |
| Δ pAi | | 0,3 | 1,47E-32 | 1,1488E-22 | 5,8424E-19 | 1,4886E-17 | 1,4886E-17 | 5,8424E-19 | | | |
| Δ pAi | | 0,35 | 8,62E-39 | 1,4784E-28 | 1,5457E-24 | 3,6958E-23 | 1,3394E-23 | 4,197E-26 | | | |
| Δ pAi | | 0,4 | 2,09E-45 | 5,2308E-35 | 7,6438E-31 | 1,1224E-29 | 7,6438E-31 | 5,2308E-35 | | | |

aff affected Individuals
 # non aff non affected Individuals
 pAi non aff allele frequency in non affected Individuals
 Δ pAi % Difference in allele frequency between affected and non-affected individuals

Figure 3 (I)



p-VALUE DISTRIBUTION

| # aff | 500 | | | | | | | | | | |
|--------------|-------------|----------|------------|------------|------------|------------|------------|--|--|--|--|
| # non aff | 500 | | | | | | | | | | |
| | pAI non aff | 0 | 0,1 | 0,2 | 0,3 | 0,4 | 0,5 | | | | |
| Δ pAI | 0,05 | 8E-13 | 0,00072323 | 0,00741865 | 0,0169842 | 0,02371865 | 0,02516449 | | | | |
| Δ pAI | 0,1 | 1,07E-24 | 3,7948E-10 | 2,4176E-07 | 2,7579E-06 | 6,9879E-06 | 6,9879E-06 | | | | |
| Δ pAI | 0,15 | 3,81E-37 | 1,0719E-18 | 5,8344E-14 | 4,2622E-12 | 1,8601E-11 | 1,1611E-11 | | | | |
| Δ pAI | 0,2 | 2,96E-50 | 5,0895E-29 | 1,6881E-22 | 6,9321E-20 | 3,7441E-19 | 6,9321E-20 | | | | |
| Δ pAI | 0,25 | 4,27E-64 | 7,2043E-41 | 7,7528E-33 | 1,194E-28 | 4,3462E-29 | 7,6438E-31 | | | | |
| Δ pAI | 0,3 | 9,7E-79 | 3,9328E-54 | 6,3017E-45 | 1,9429E-41 | 1,9429E-41 | 6,3017E-45 | | | | |
| Δ pAI | 0,35 | 2,91E-94 | 8,8513E-69 | 8,7878E-59 | 2,3478E-55 | 1,8838E-56 | 1,1206E-62 | | | | |
| Δ pAI | 0,4 | 9,5E-111 | 7,7199E-85 | 1,8063E-74 | 1,4484E-71 | 1,8063E-74 | 7,7199E-85 | | | | |

| # aff | 150 | | | | | | | | | | |
|--------------|-------------|----------|------------|------------|------------|------------|------------|--|--|--|--|
| # non aff | 850 | | | | | | | | | | |
| | pAI non aff | 0 | 0,1 | 0,2 | 0,3 | 0,4 | 0,5 | | | | |
| Δ pAI | 0,05 | 2,16E-20 | 0,00984614 | 0,04896055 | 0,08358651 | 0,10417953 | 0,11025423 | | | | |
| Δ pAI | 0,1 | 2,01E-39 | 5,571E-07 | 0,00010149 | 0,00058665 | 0,00119145 | 0,00139743 | | | | |
| Δ pAI | 0,15 | 1,11E-58 | 2,7555E-13 | 8,462E-09 | 2,9851E-07 | 1,2395E-06 | 1,6229E-06 | | | | |
| Δ pAI | 0,2 | 3,27E-78 | 2,1683E-21 | 3,2211E-14 | 1,1049E-11 | 1,111E-10 | 1,5638E-10 | | | | |
| Δ pAI | 0,25 | 4,96E-98 | 4,4952E-31 | 6,5226E-21 | 3,1015E-17 | 2,5169E-16 | 1,1763E-15 | | | | |
| Δ pAI | 0,3 | 3,7E-118 | 3,6987E-42 | 8,129E-29 | 6,9335E-24 | 5,4331E-22 | 6,5657E-22 | | | | |
| Δ pAI | 0,35 | 1,4E-138 | 1,6797E-54 | 7,1058E-38 | 1,2938E-31 | 2,9415E-29 | 2,5869E-29 | | | | |
| Δ pAI | 0,4 | 2,4E-159 | 5,4915E-68 | 4,8846E-48 | 2,1003E-40 | 1,3332E-37 | 6,8178E-38 | | | | |

aff affected individuals
 # non aff non affected individuals
 pAI non aff allele frequency in non affected individuals
 Δ pAI % Difference in allele frequency between affected and non-affected individuals

Figure 3 (II)



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ALLELIC ASSOCIATION
3,000 MARKERS MAP

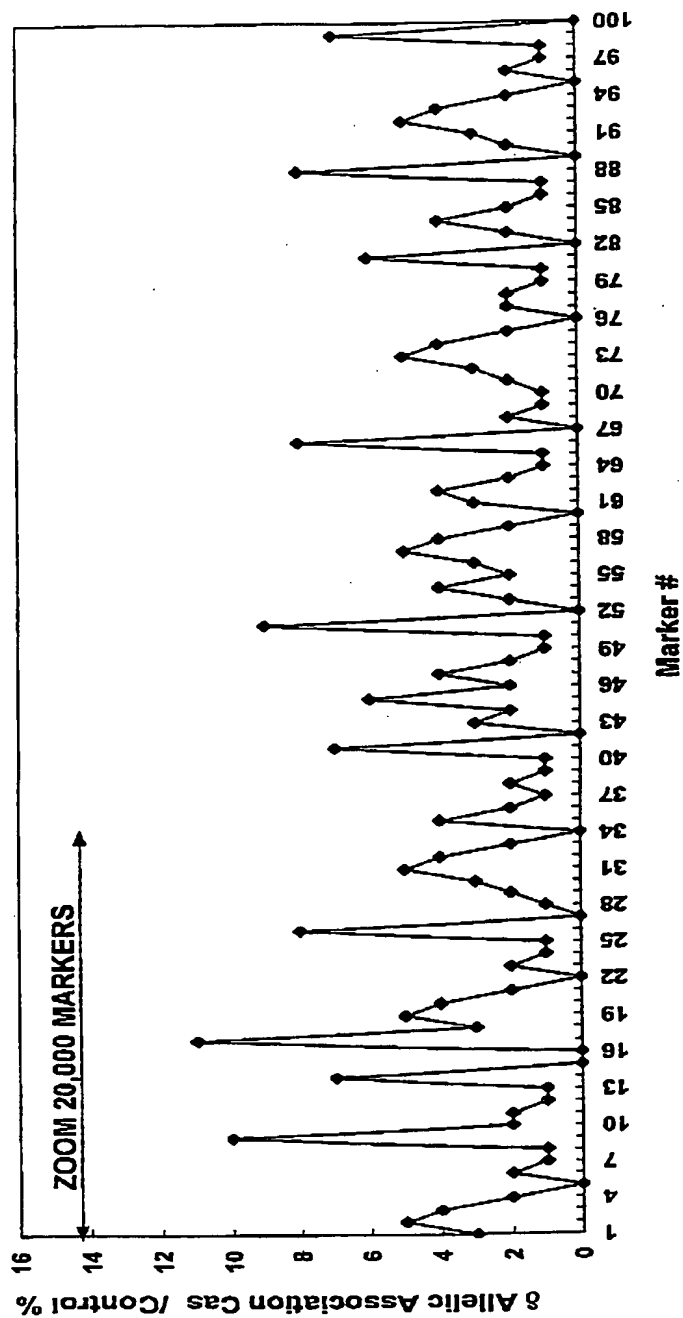


Figure 4



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ALLELIC ASSOCIATION
20,000 MARKERS MAP

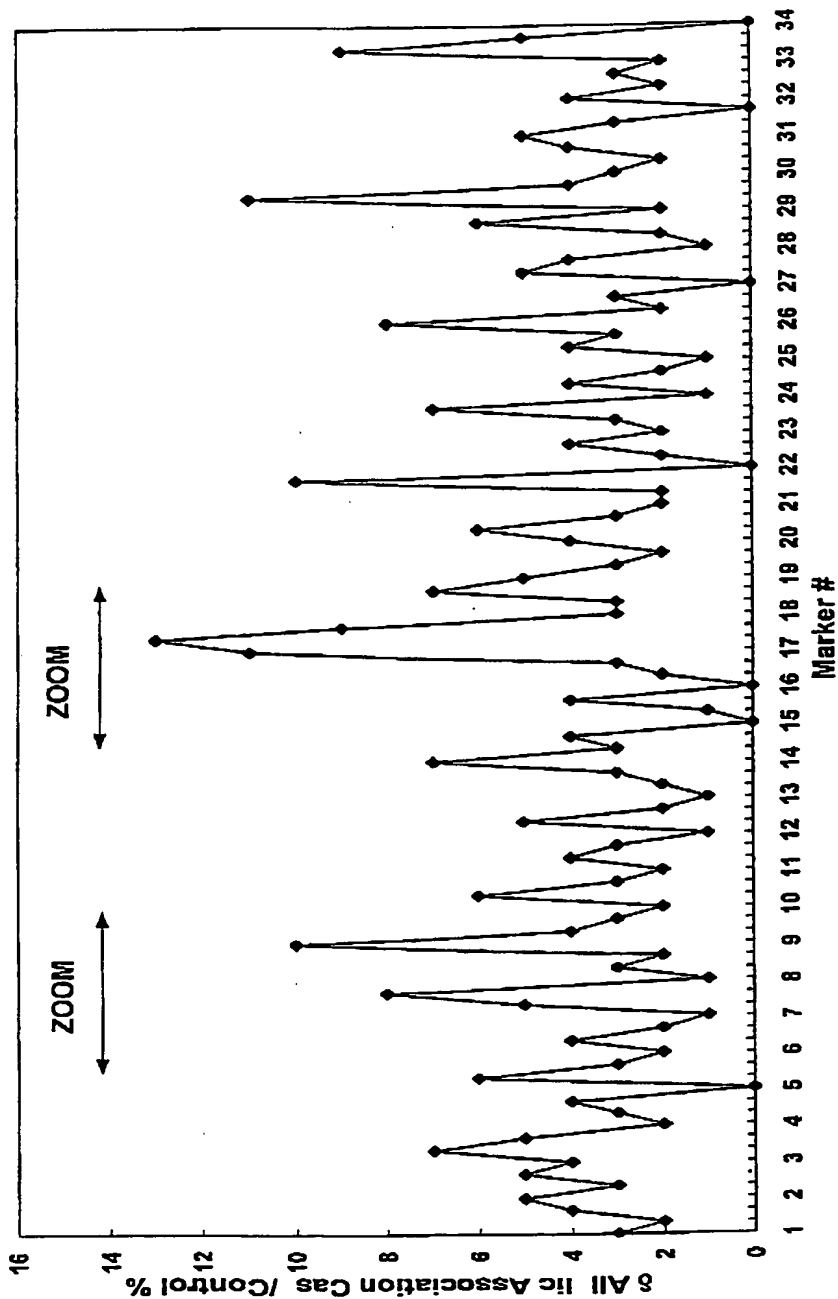


Figure 5



ALLELIC ASSOCIATION 60,000 MARKERS MAP

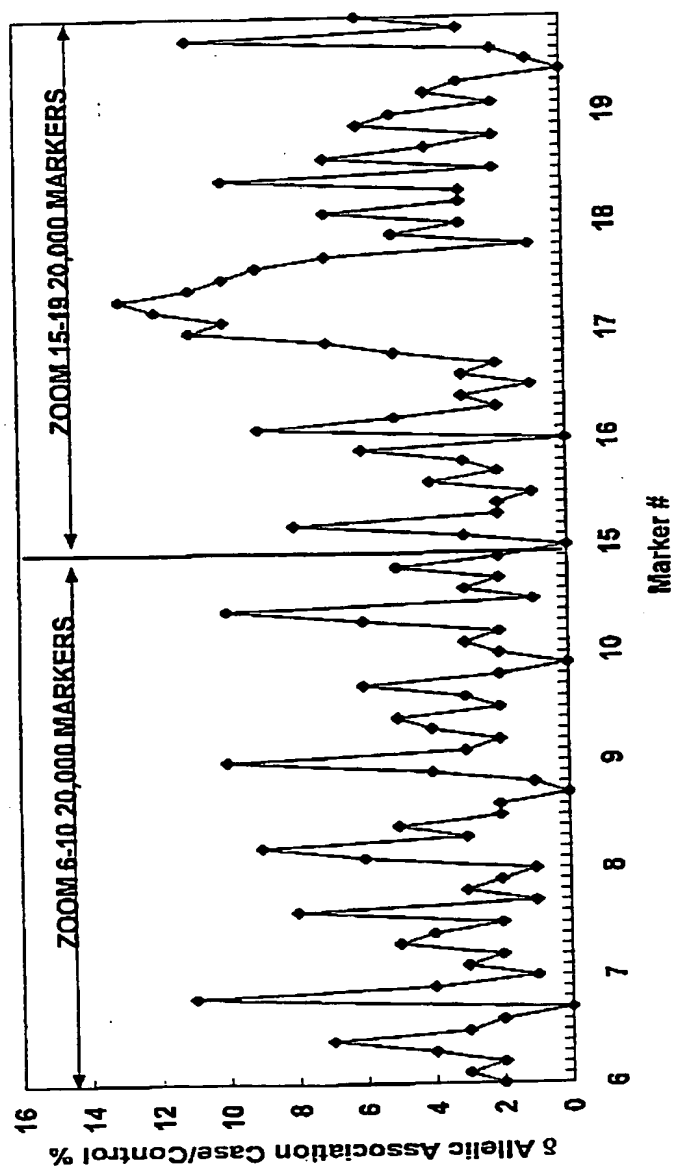


Figure 6



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APO E REGION HAPLOTYPE FREQUENCY ANALYSIS

| POPULATIONS | | AD CASES (225) | | | | AD CONTROLS (248) | | | |
|-------------|----------|----------------|----------|----------|-----------------------|-------------------|-------|----------|-------|
| markers | 99-366 | 99-344 | 99-359 | 99-355 | haplotype frequencies | | odds- | P value | |
| p value | 3,01E-01 | 1,11E-01 | 6,63E-01 | 1,38E-01 | cases | controls | ratio | | |
| haplotype 1 | C | G | | | 0,404 | 0,308 | 1,52 | 3,05E-03 | *** |
| haplotype 2 | | G | A | | 0,203 | 0,165 | 1,29 | 1,24E-01 | * |
| haplotype 3 | | | G | G | 0,375 | 0,306 | 1,36 | 2,83E-02 | ** |
| haplotype 4 | C | | A | | 0,264 | 0,209 | 1,36 | 5,95E-02 | ** |
| haplotype 5 | | G | | A | 0,116 | 0,071 | 1,70 | 1,64E-02 | ** |
| haplotype 6 | C | | | A | 0,15 | 0,129 | 1,19 | 3,59E-01 | * |
| haplotype 7 | T | | G | G | 0,225 | 0,122 | 2,09 | 4,76E-05 | ***** |
| haplotype 8 | T | A | G | G | 0,228 | 0,108 | 2,44 | 2,05E-06 | ***** |

Figure 7



APO E REGION HAPLOTYPE SIMULATION POPULATION : 225 CASES vs 248 CONTROLS

| Haplotype | 4 Markers | | | | haplotype frequencies | | odds-ratio | pvalue |
|-----------|------------|------------|------------|------------|-----------------------|----------|------------|----------------|
| | A | T | G | G | cases | controls | | |
| | 99-344/439 | 99-366/274 | 99-359/308 | 99-355/219 | 0,228 | 0,108 | 2,44 | 2,05E-06 ***** |

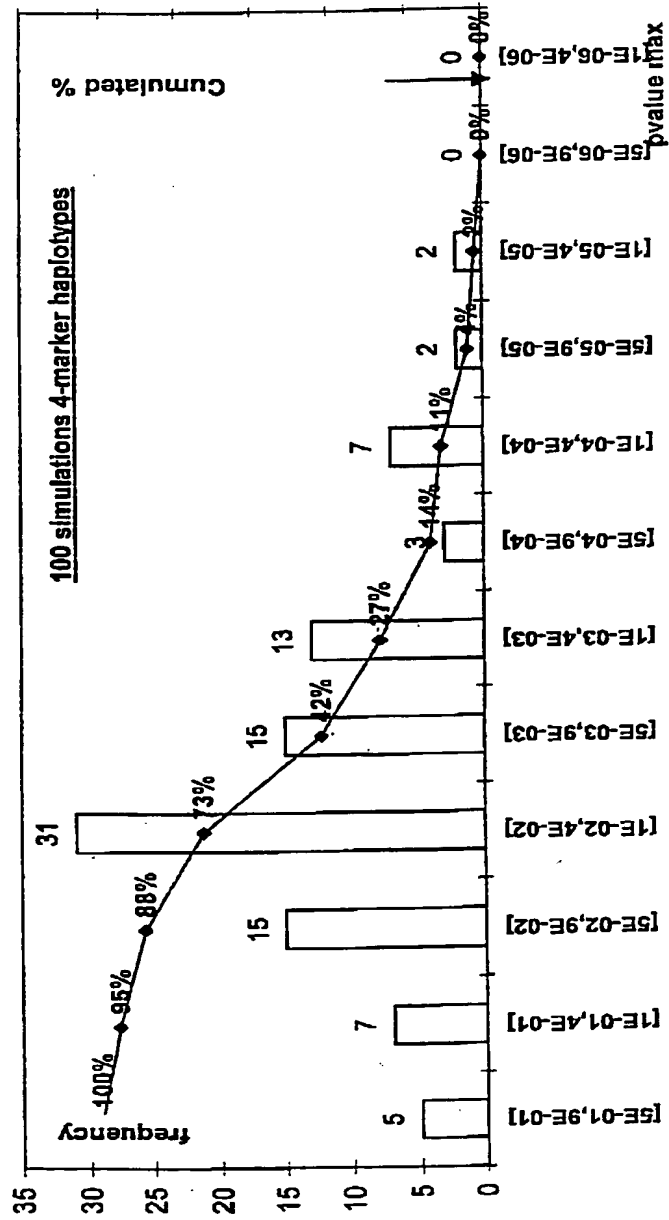
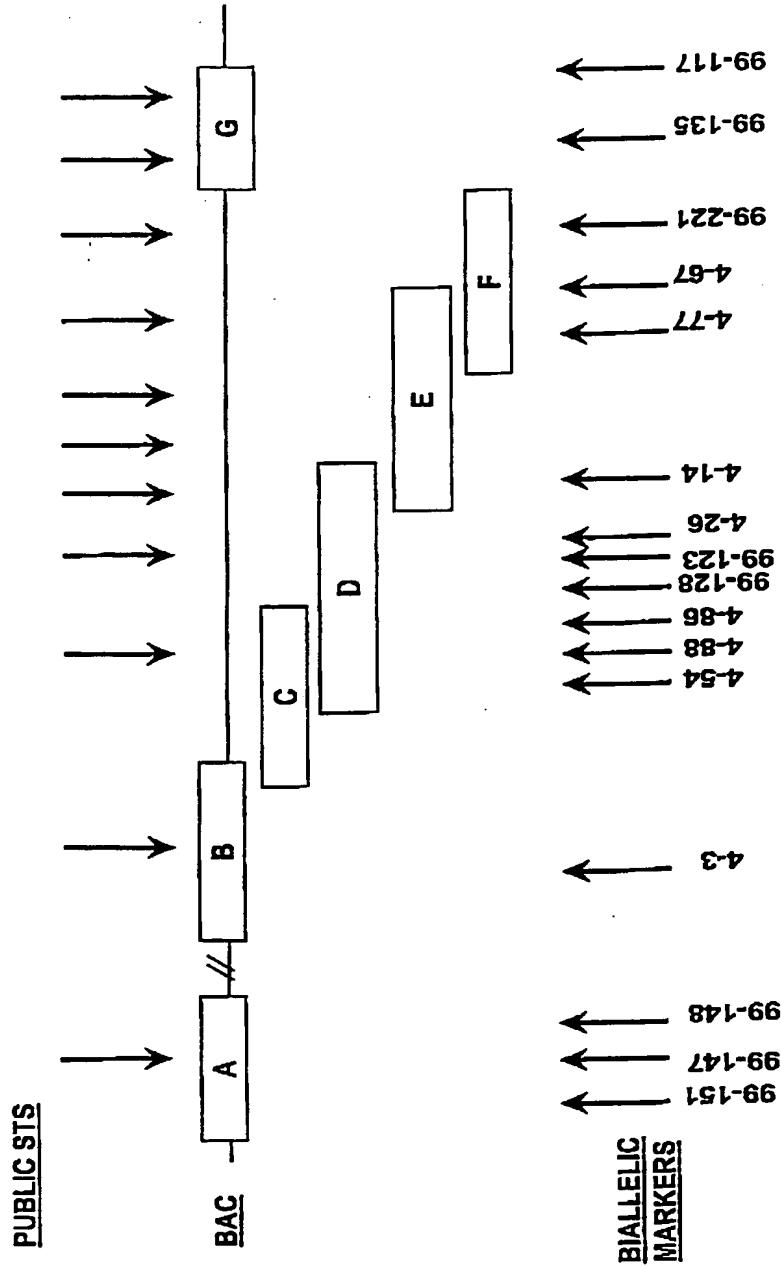


Figure 8

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09058200 - 00000000

PROSTATE CANCER ASSOCIATION STUDIES (FIRST SCREENING)

| Population Sample size | PROSTATE CANCER | NON AFFECTED |
|-------------------------------|--|---------------------|
| | CASES = 112 | CONTROLS=76 |
| Population Characteristics | 35 sporadic cases + 77 familial cases | > 65 years PSA<4 |
| | | |

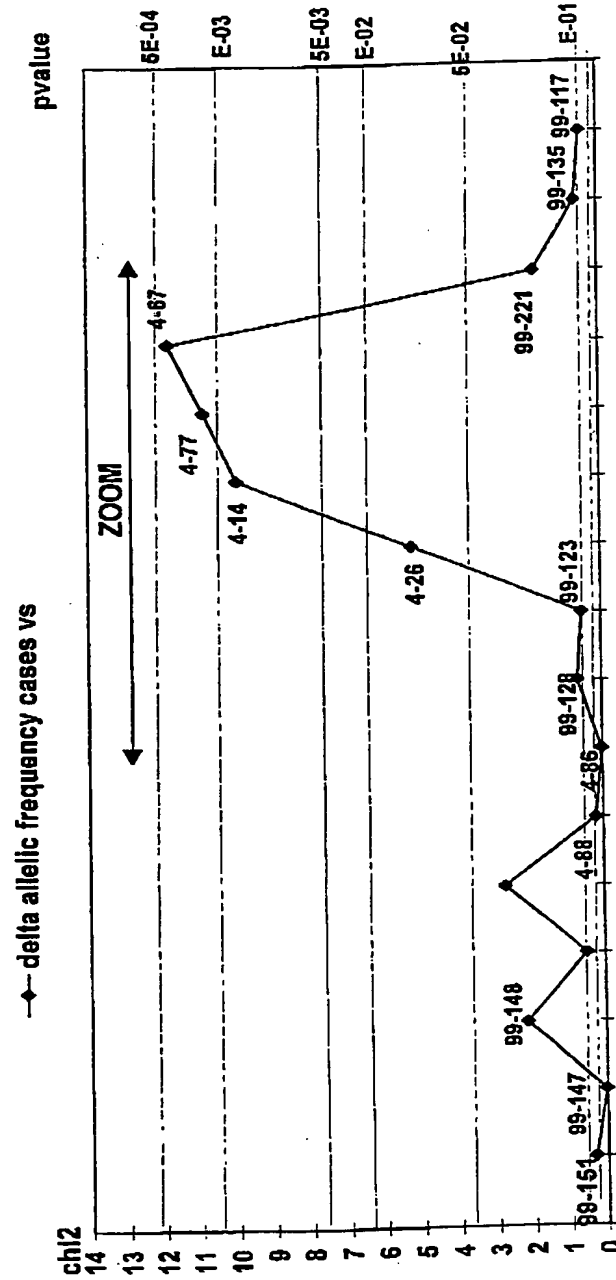


Figure 10



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PROSTATE CANCER ASSOCIATION STUDIES (ZOOM)

| | PROSTATE CANCER | NON-AFFECTED |
|--------------------------------|---|---------------------|
| | CASES (185) | CONTROLS (104) |
| characteristics of populations | 47 sporadic cases + 138 familial cases | > 65 years PSA<4 |

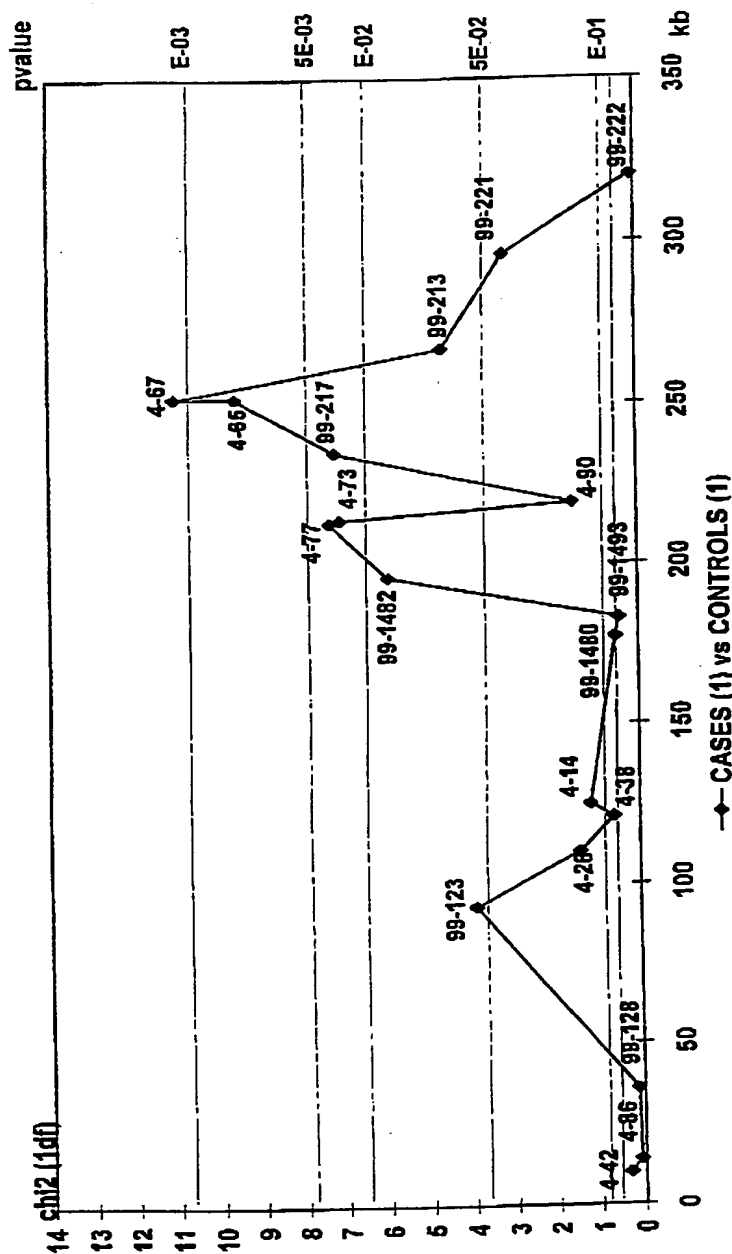


Figure 11



PROSTATE CANCER HAPLOTYPE SIMULATIONS (100 ITERATIONS)

| markers | 4-14 | 4-77 | 99-217 | 4-67 | 99-213 | 99-221 | haplotype frequencies | | relative risk | pvalue |
|-----------|------|------|--------|------|--------|--------|-----------------------|----------|---------------|----------|
| | | | | | | | cases | controls | | |
| haplotype | C | G | T | T | G | A | 0,117 | 0,013 | 10,06 | 9,00E-07 |

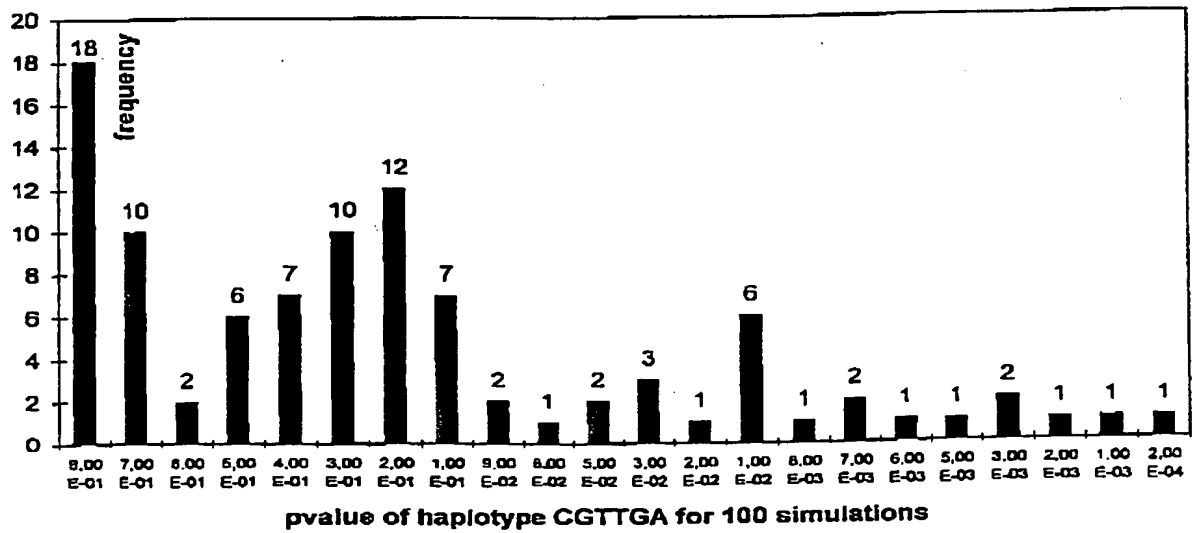
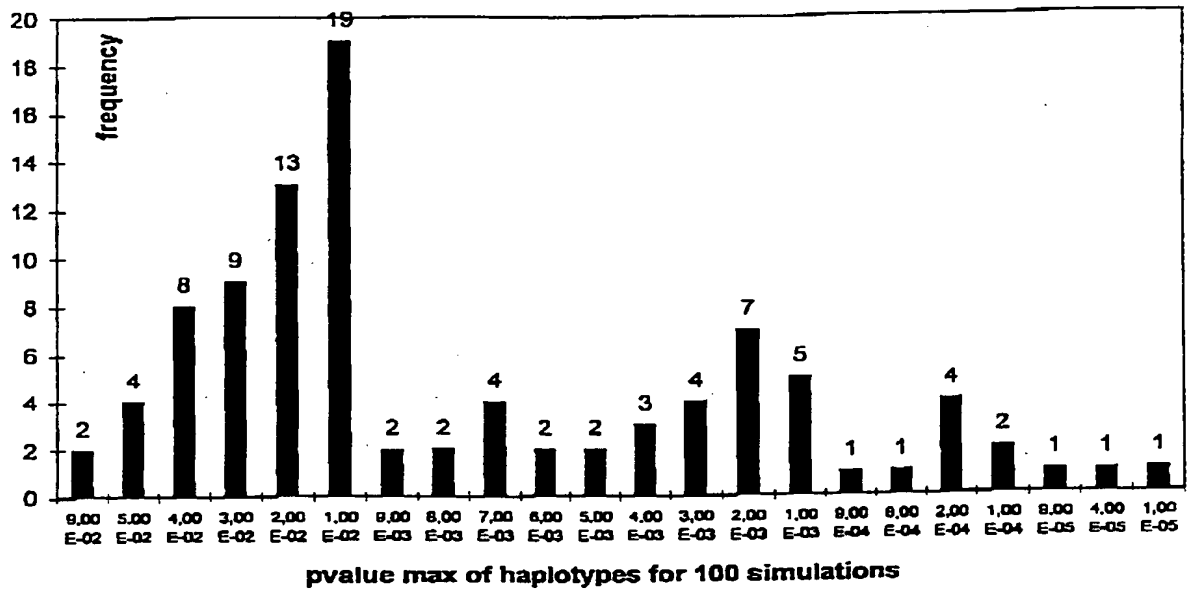


Figure 13



AVERAGE LD PATTERN GENOMIC HETEROGENEITY

| Recombination rate | Lower A | Higher B |
|--|---------------|----------------|
| Nb markers | 89 | 69 |
| All SNP | 0.61 (749) | 0.42 (1190) |
| Rare < 0.2 Rare vs rare | 0.75 (65) | 0.17 (158) |
| Frequent > 0.2 Frequent vs frequent | 0.51 (410) | 0.49 (544) |
| Rare vs frequent | 0.72 (274) | 0.41 (488) |

FIGURE 14

**Exonic/nonexonic LD**

| | Nb pairs | Average intermarker distance | Average LD |
|-------------------|----------|------------------------------|------------------|
| Exonic SNPs | 36 | 26 kb | 0.65 ± 0.021 |
| Non exonic SNPs | 60 | 36 kb | 0.48 ± 0.018 |
| Exonic/Non exonic | 96 | 32 kb | 0.60 ± 0.015 |

FIGURE 15



FIGURE 16 A



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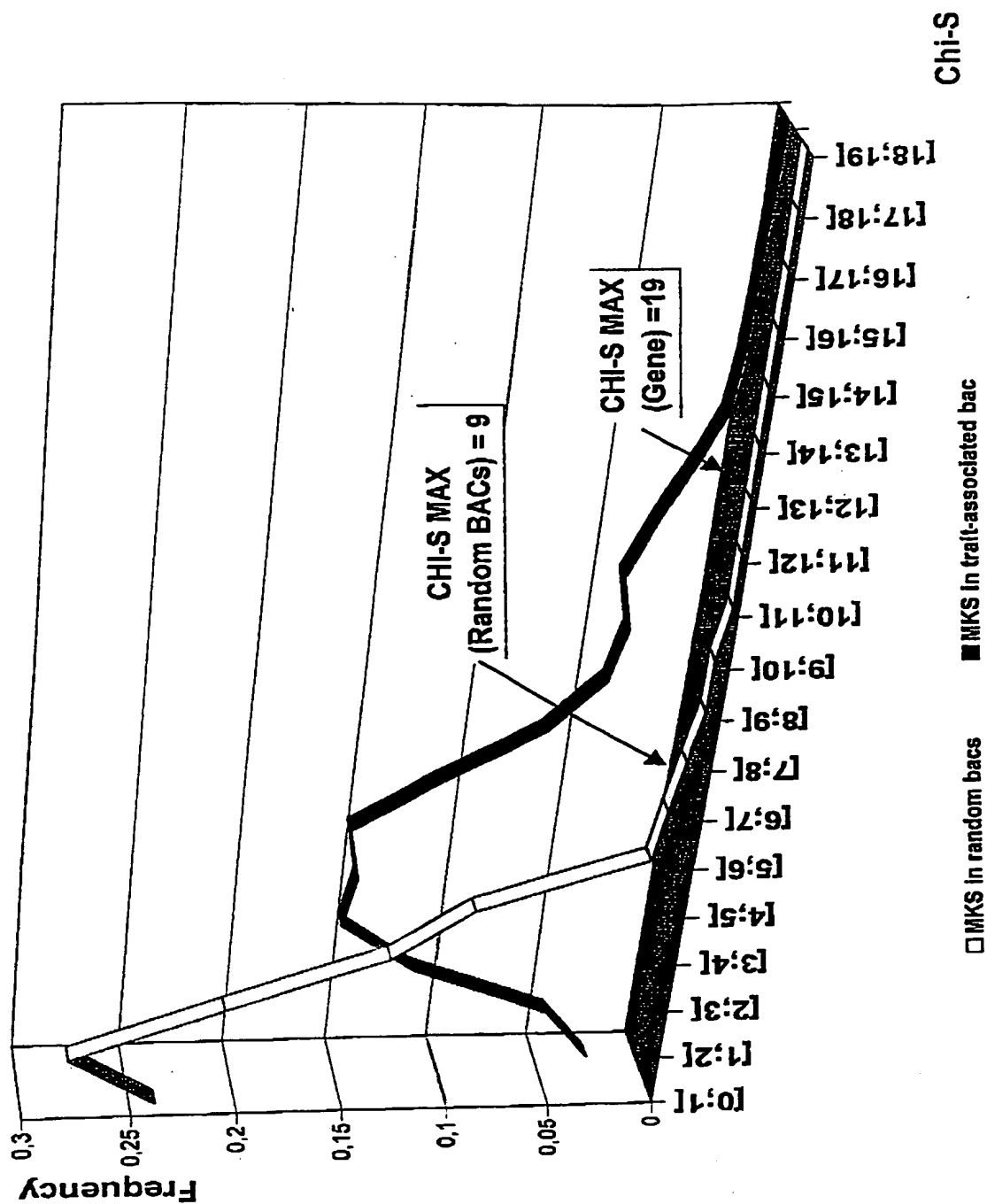


FIGURE 16B



09858289.032893

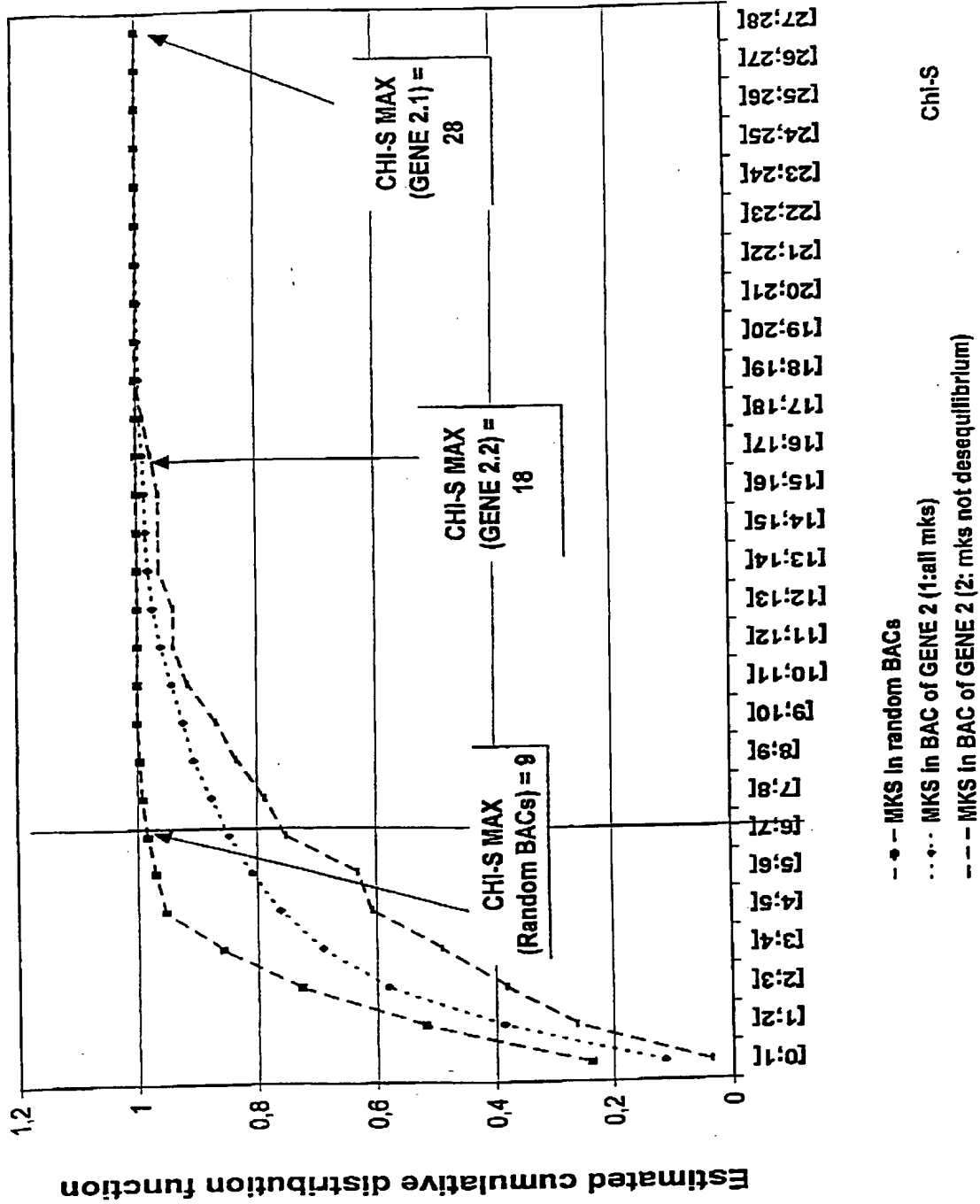


FIGURE 17A



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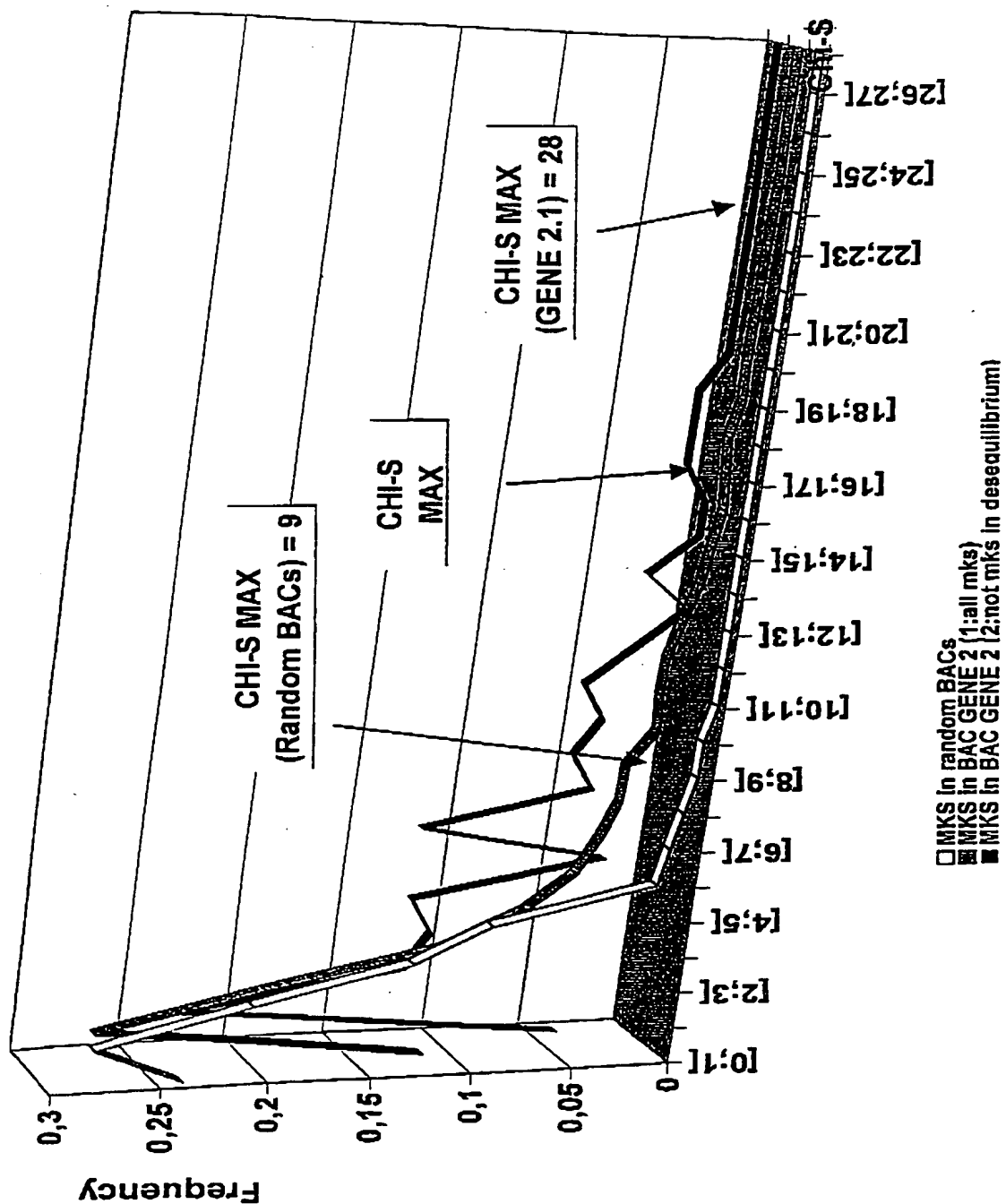


FIGURE 17 B

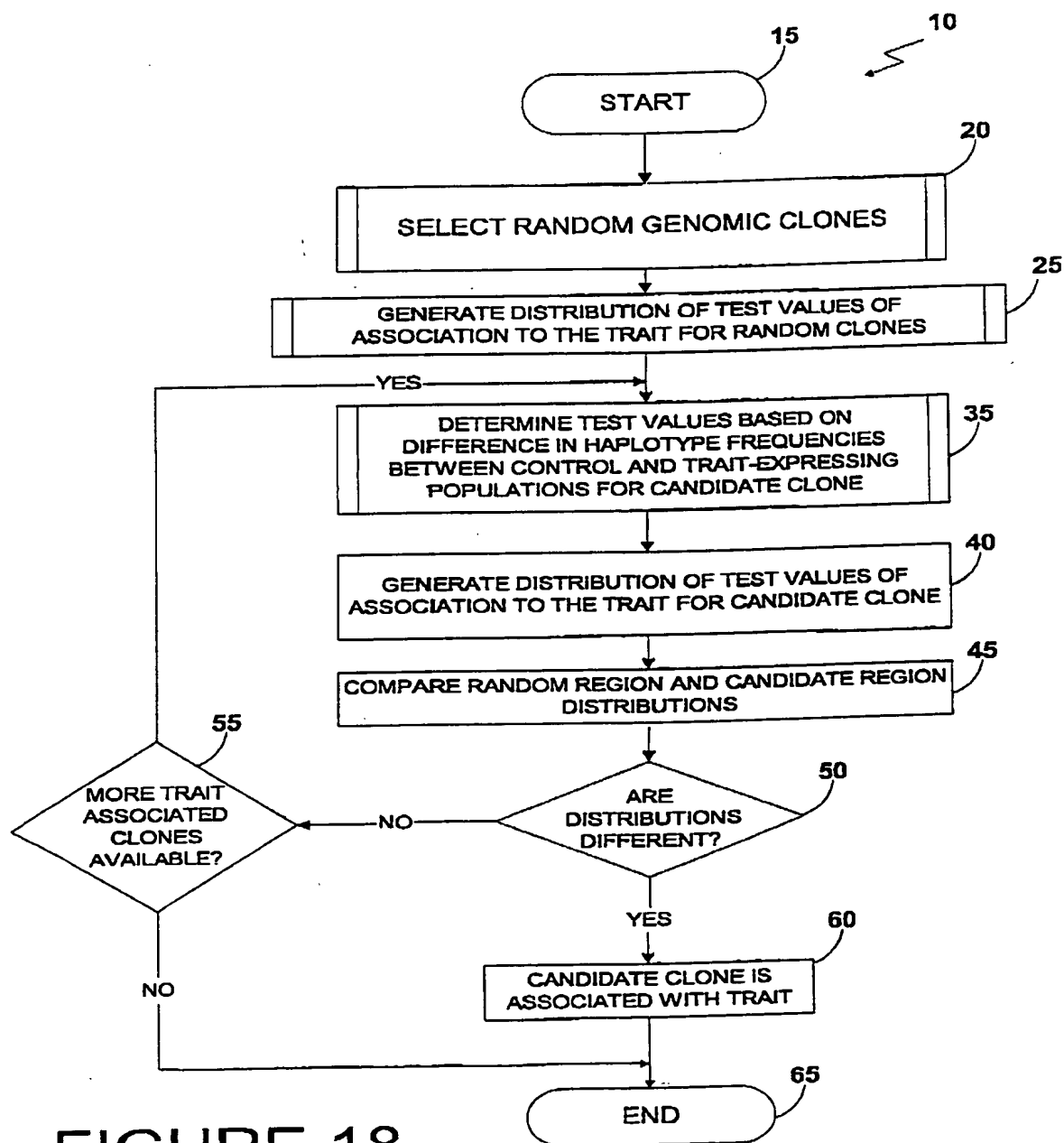


FIGURE 18

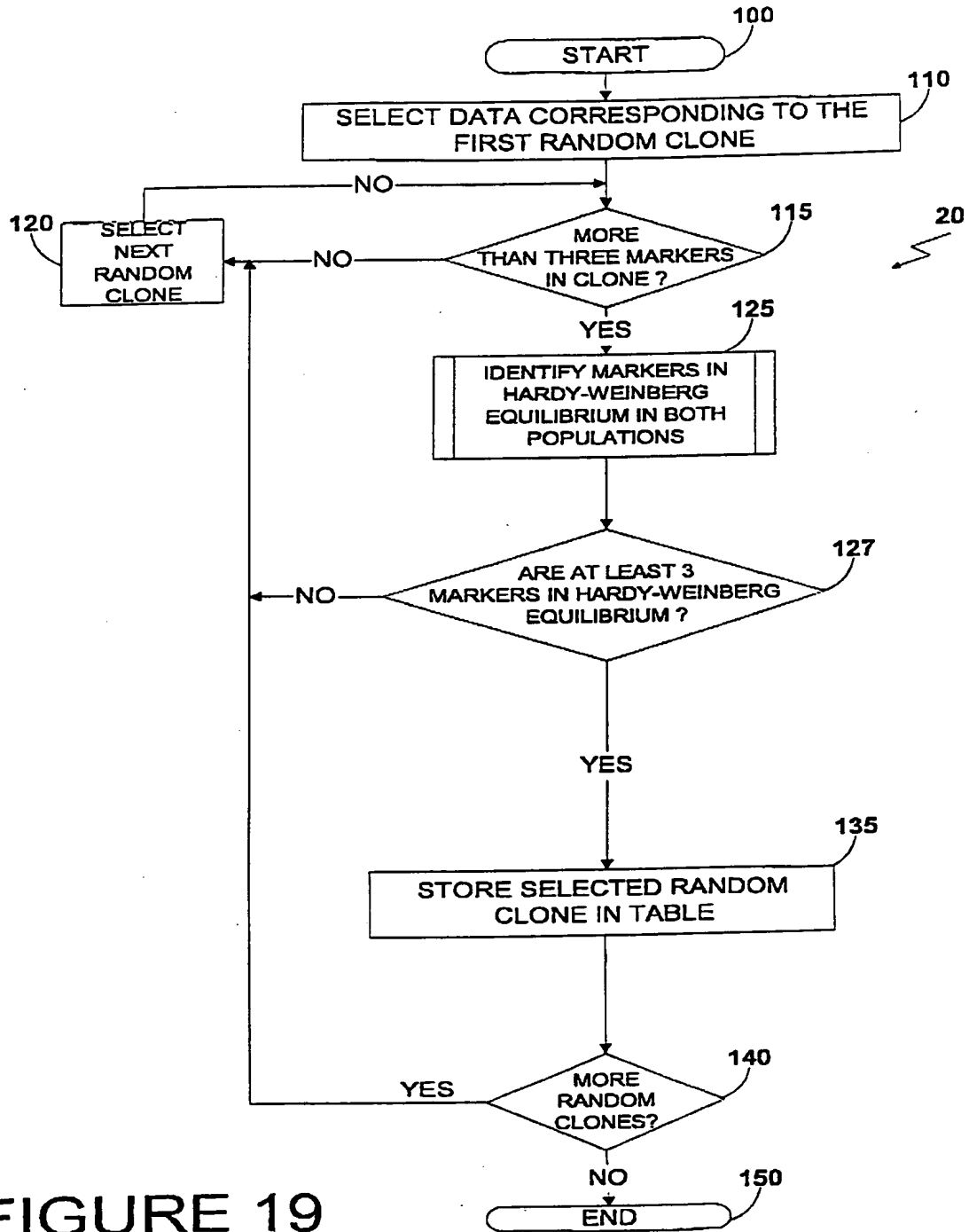


FIGURE 19

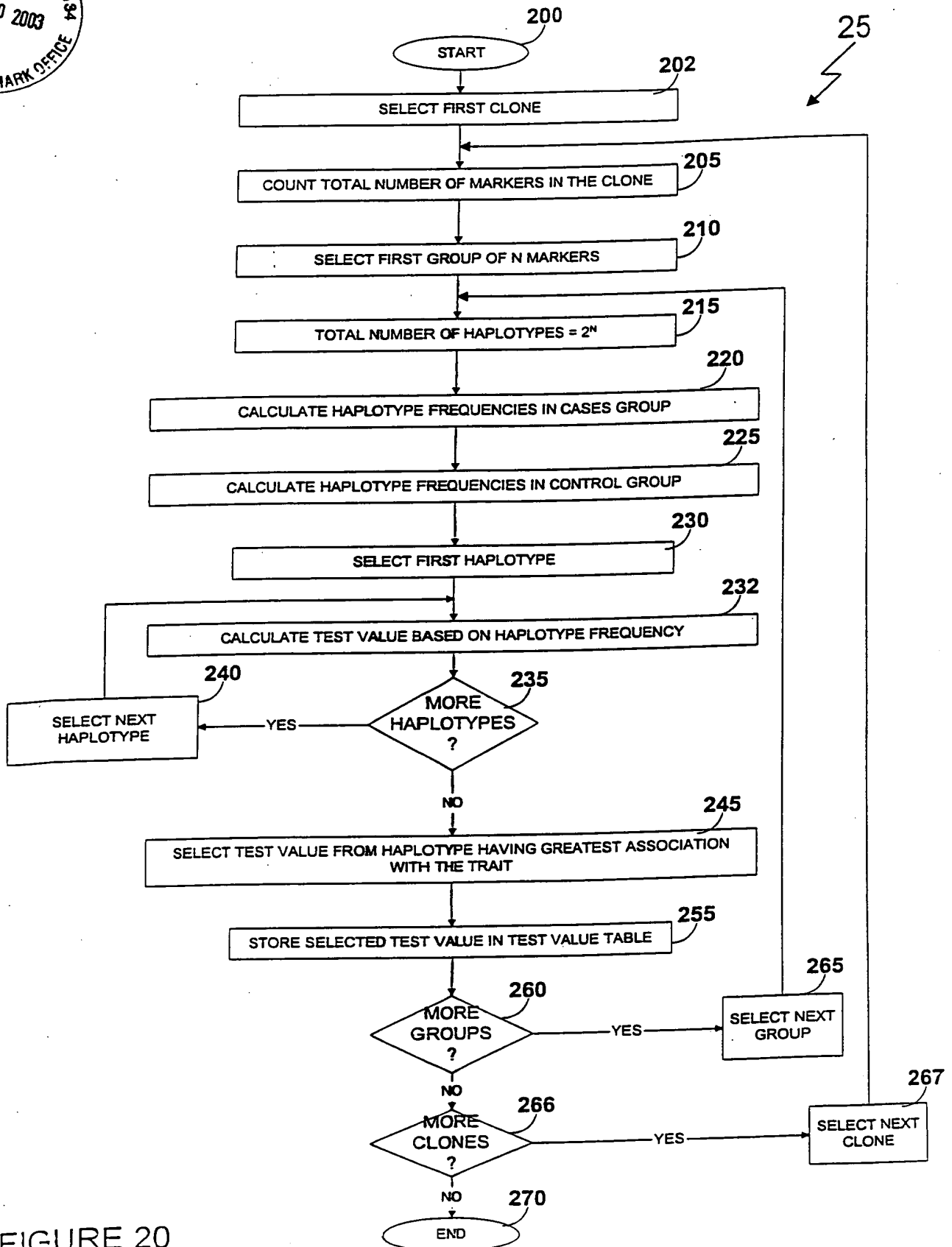
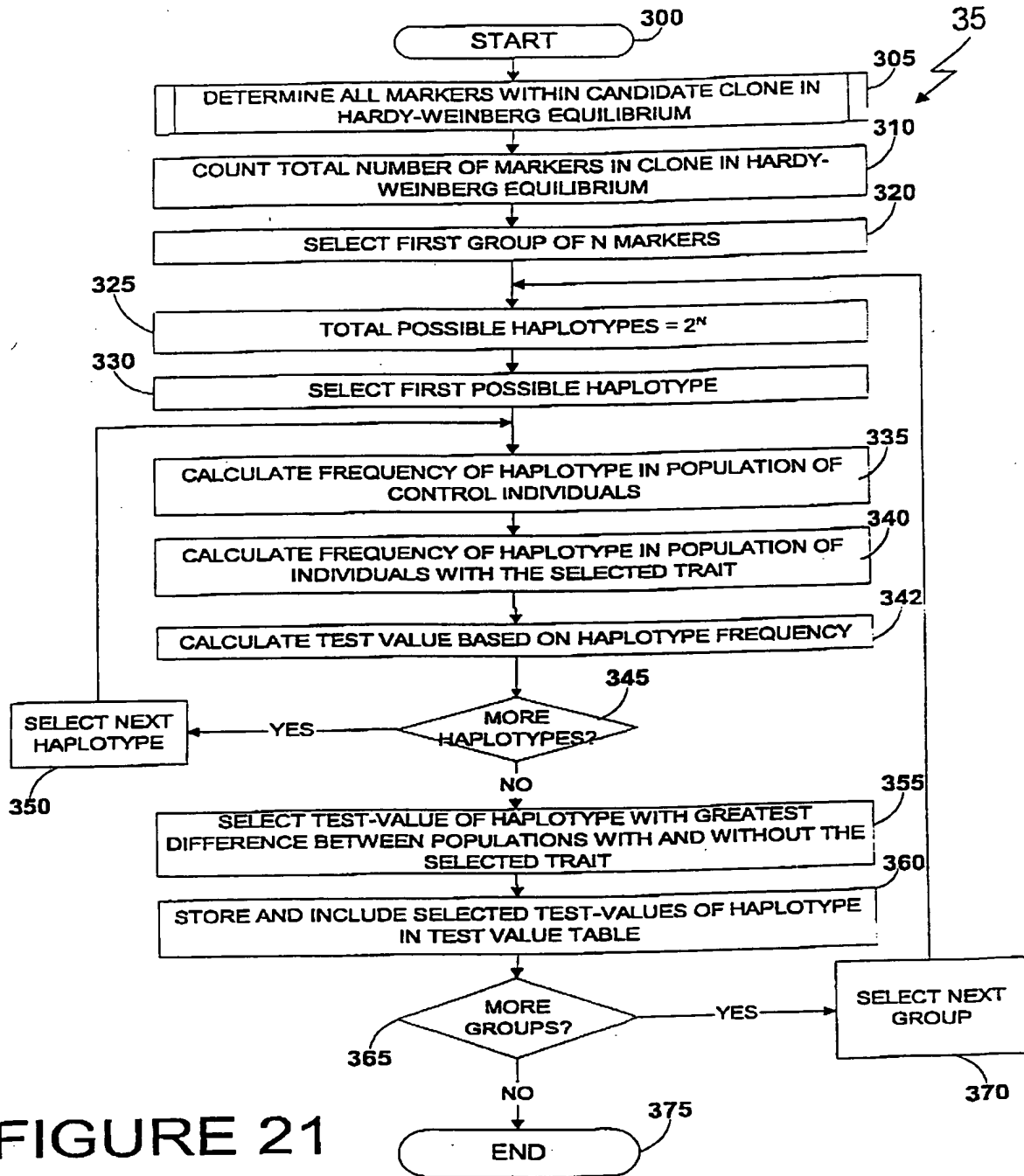


FIGURE 20



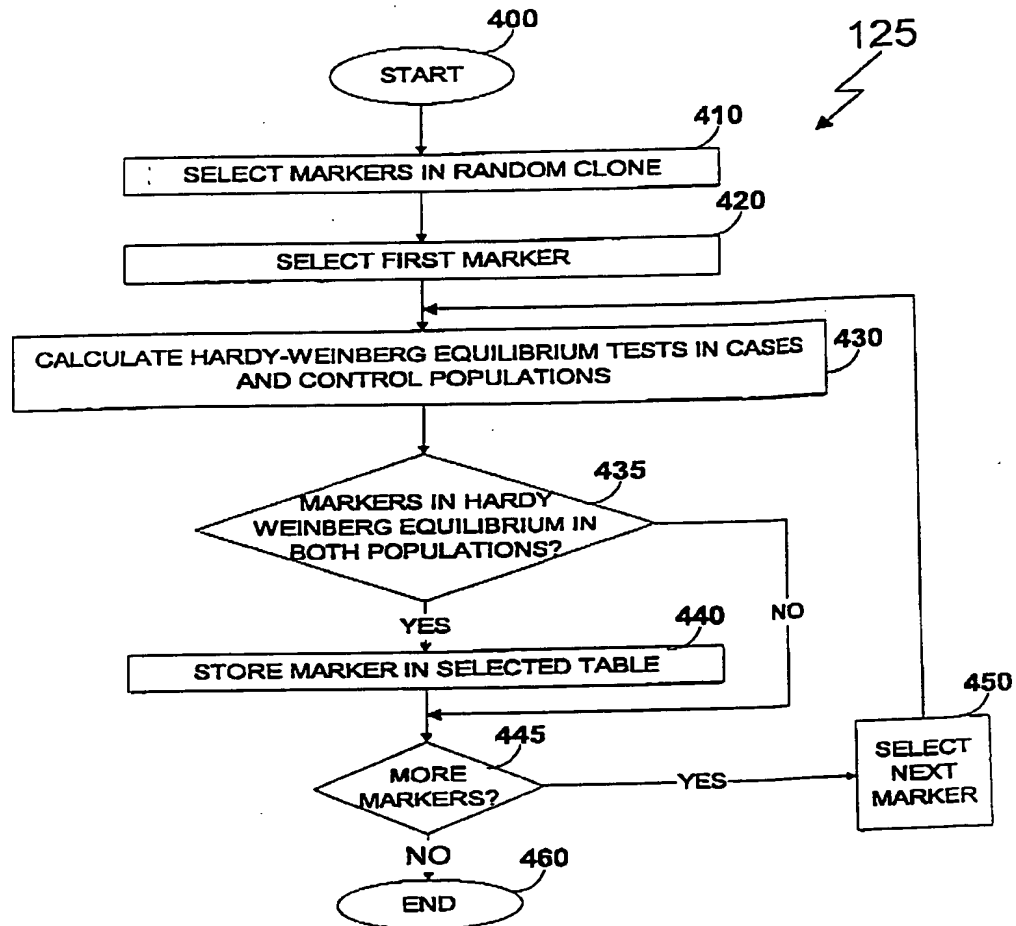


FIGURE 22

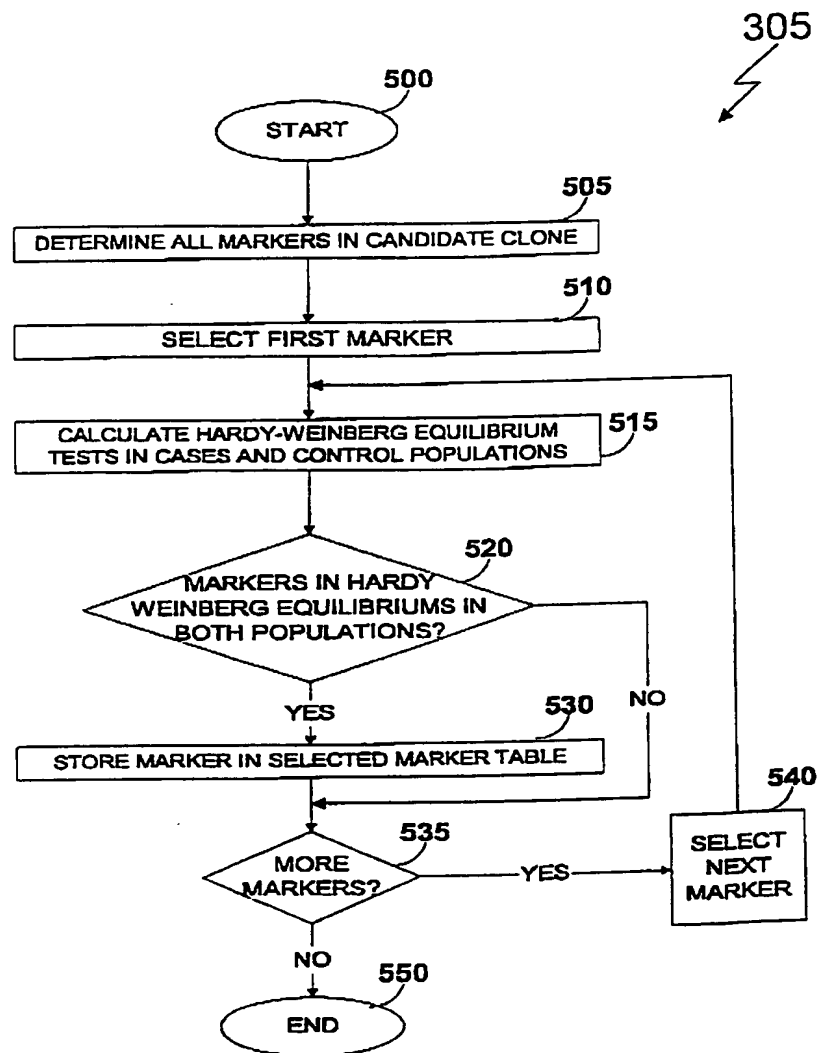


FIGURE 23

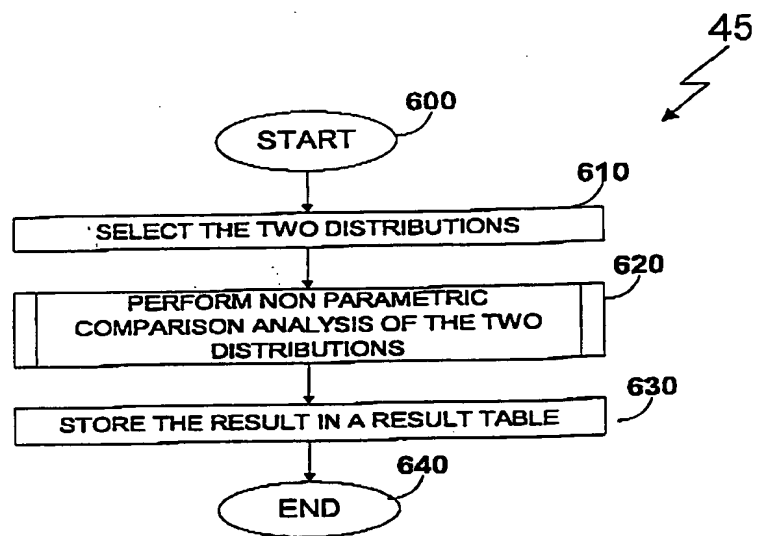


FIGURE 24

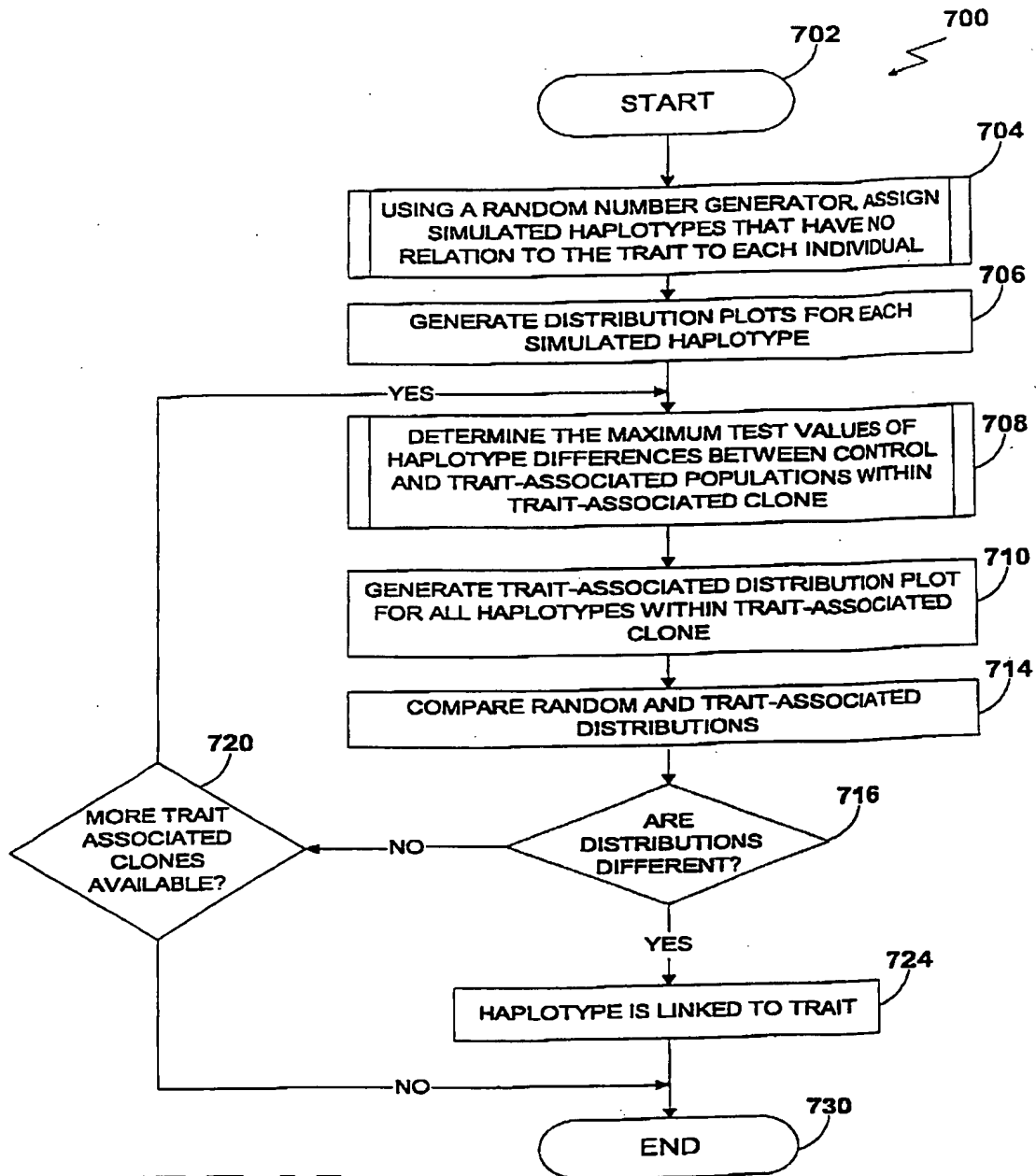


FIGURE 25